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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/977,155	10/12/2001	Joachim Herz	UTSD:0862	3854

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EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/977,155	**Applicant(s)** HERZ ET AL.	
	Examiner Lisa V. Cook	**Art Unit** 1641	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 June 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☒ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *NONE*.
   Claim(s) objected to: *NONE*.
   Claim(s) rejected: *1-20*.
   Claim(s) withdrawn from consideration: *NONE*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

LONG V. LE 07/25/05
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Request for Reconsideration

1. Applicants' response to the Final Office Action mailed 5/18/05 and the Advisory Action mailed 6/16/05 is acknowledged (Fax dated June 25, 2005). Currently claims 1-20 are pending and under consideration.

Non-Compliant Amendement

2. The proposed amendment filed June 25, 2005 has been considered but was not deemed allowable because the cited reference of Willnow anticipates the claimed subject matter (see response to argument herein). Further the amendment was not filed in compliance with 37 CFR 1.121. Therefore it has not been entered.

3. The proposed amendment to claim 1, filed 6/25/05 on page 3 was entered for discuss only (non-compliant under 37 CFR 1. 121(c)). The proposed amendment does not place the application in condition for allowance and has been specifically addressed herein.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I. Claims 1-9 and 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Willnow et al. (The Journal of Biological Chemistry, Vol.269, No.22,15827-15832, 1994).

Willnow et al. teach methods involving LRP-mini receptors . See abstract.

The LRP-mini receptor comprises 11 complement-type repeats (LDL receptor ligand – polypeptide) and one EGF precursor homologous domain (region IV) is fused to the carboxyl-terminal segment of LRP (six EGF repeats, transmembrane segment, and the cytoplasmic tail). See page 5828, 2nd column, 1ts paragraph, and figure 1. Region IV contains a proteolytic site, which allows for protease digestion into an 80kDa amino-terminal and an 85kDa carboxyl-terminal fragment (C-terminal tail).

The LRP regions were prepared via SDS gel electrophoresis and transferred to nitrocellulose (solid-phase affinity adsorption). Polyclonal anti-LRP antibodies directed against the cytoplasmic tail of LRP and ^{125}I goat anti-rabbit IgG (affinity tag) was utilized in Western blotting procedures to detect the mini receptors membrane extracts from the cell lines. Bottom of page 15828 to 15829 and figure 2.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

II. Claims 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Willnow et al. (The Journal of Biological Chemistry, Vol.269, No.22,15827-15832, 1994) in view of Herz (Neuron, Vol29, pages 571-581).

Please see Willnow et al. as set forth above.

Willnow et al. differs from the instant invention in not teaching all the possible LDL receptor (namely LRP, LRP1b, megalin, LDLR, VLDLR,ApoER2, MEGF7, LRP5, LRP6, and LR11).

However, Herz discloses the core members of the LDL receptor gene. See abstract and figure 1. Herz further teaches each LDL possible role and involvement in cellular events. See Table 1. The core members of the LDL receptor gene family include the LDL receptor, LRP, megalin, VLDL, ApoER2, LrP1b, and MEGF7. See page 571, 1st column, 2nd paragraph. Herz et al. disclose that these seven core members of the LDL receptor gene family are "structurally closely related cell surface receptor".

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use various known LDL receptor equivalents having similar structures and found native to the membrane as taught by Herz in the method of Willnow et al. because Herz taught that the LDL receptor gene family consists of seven structurally related cell surface receptors (LDL receptor, LRP, megalin, VLDL, ApoER2, LrP1b, and MEGF7). See abstract. Therefore the analysis of any of the known equivalent receptors taught by Herz in the method of Willnow et al. would have been obvious because the receptors would perform the same function in the same manner as the receptors found in Willnow et al.

In other words the behavior of one compound predicts the behavior of equivalents absent evidence to the contrary. Further, applicant has not set forth reasons for the utility of any particular receptor.

Accordingly, obviousness is based on the similarity of structure, function, and similar properties. In re Payne, 606 F.2d 303, 203, USPQ 245, 254-55 (CCPA 1979).

Response to Arguments

Applicant contends that LRP is known to be naturally proteolyzed at the extra cellular N-terminal site to produce two subunits. A 85 kd membrane spanning beta subunit and a larger 515 kd N-terminal alpha subunit that remains attached to the smaller C-terminal beta subunit (Herz et al. 1990, EMBO J 9, 1769-1776). Because the instant invention is directed to proteolytic processing events that need to occur at intramembranous or cytoplasmic sites resulting in the release of the cytoplasmic tail into the cytoplasm , the instantly claimed invention is novel.

This argument was carefully considered but not found persuasive because the features upon which applicant relies (i.e., cleavage at specific intramembranous or cytoplasmic sites) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims merely require a protease that cleaves a domain and releases a tail from the membrane. (See claim 1). Therefore, the prior art teaching of Willnow et al. involving the proteolytic separation of LRPs reads on the release of a tail from the membrane (N terminal extra cellular domains comprising the smaller C-terminal tails).

Applicant argues that although Willnow et al. teach the utility of an anti-LRP antibody directed against the cytoplasmic tail the carboxy terminal is released from the membrane by biochemical extraction after protease exposure. This argument was carefully considered but not found persuasive because the claimed method employs "comprising", which is open language allowing for addition process steps in the claimed method. Further, the claim language merely requires the release of the tail [reading on the 515 kd N-terminal alpha subunit that remains attached to the smaller C-terminal beta subunit (Herz et al. 1990, EMBO J 9, 1769-1776)] from the membrane [LRP receptor transmembrane]. Willnow et al. disclose this type of separation and is therefore maintained.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., protease product consisting of only the C-terminal tail) are not recited in the rejected claim(s).

Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Specifically, Willnow et al. disclose LRPs subsets that include the cytoplasmic tail as well as the detection of the cytoplasmic tail. For example on page 15828, 2nd column, middle section and figure 1 - regions II and IV are fused to the membrane (carboxyl-terminal segment) and the cytoplasmic tail (cytoplasmic segments of LRP).

Proteolytic processing resulting in a separation of the LRP within the domain to produce a N-terminal and C-terminal product is seen on page 15829 1st column. In one embodiment, the cytoplasmic tail of LRP is detected with polyclonal anti-LRP antibodies by Western blotting. See page 15828 2nd column 2nd paragraph.

On page 15829, 1st column, 1st paragraph – Region IV is taught to be cleaved by intracellular proteases that cleave LRP at a tetrabasic site in the eighth EGF precursor domain and these proteases can process LRP into a 80kDa amino terminal and a 85kDa carboxyl-terminal fragment (lanes 2 and 4 of figure 2A). Accordingly, Willnow et al. teach proteolysis procedures that produce a N-terminal and C-terminal of a LDL receptor domain fused to a c-terminal tails and well as c-terminal tail detection.

Applicants argue that Willnow et al. do not teach protease liberation of the c-terminal tail of LDR, therefore the combination of Willnow et al. and Herz et al. cannot make the invention obvious. This argument has been carefully considered but is not found persuasive. The arguments against Willnow et al. have been addressed a priori and were not found persuasive, therefore the rejection of Willnow et al. in view of Herz et al. is maintained.

Applicant also contends that Examiner has not correctly interpreted the claim language (claim construction) because it appears that "thereby" and "wherein" (whereby) were not been given patentable weight. This argument was carefully considered but not found persuasive because the examiner has read the claims as broadly as reasonable and have afforded the term "thereby" and "wherein" (whereby) with patentable weight.

Further, it has been held that the functional "whereby" statement does not define any structure and accordingly cannot serve to distinguish. *In re Mason*, 114 USPQ 127, 44 CCPA 937 (1957).

The claims have been construed to read on contacting an LDL receptor transmembrane domain fused to a C-terminal tail with a protease that cleaves the domain and releases the tail from the membrane. Applicant argues that the cited art does not teach this method because the claim requires protease cleavage to release the tail and not some independent mechanism, such as biochemical extraction. This argument was carefully considered but not found persuasive because Willnow et al. (1994, J Biol Chem 269, 15827-15832) disclose the claimed method. Specifically the reference discloses that LRP consists of four separate regions (I, II, III, and IV) each characterized by an LDL receptor ligand and epidermal growth factor domains (Applicants LDL receptor transmembrane domain) fused to the carboxyl-terminal segment (Applicants C-terminal tail). See page 15828, 2nd column –Results and figure 1. The LRP is further taught to be cleaved by a protease at a tetrabasic site in the eight EGF domain. See page 15829 1st column 1st paragraph.

Accordingly the cited reference discloses the claimed composition (LRP- LDL receptor transmembrane domain) cleaved by a protease as claimed by Applicant. A compound (protease) and its properties are inseparable (cleavage of the LDL receptor-LRP). *In re Papesch*, 315 F.2d, 381, 137 USPQ 43 (CCPA 1963).

Willnow et al. disclose the same process of protease cleavage of LRP, therefore it anticipated the instant claims. Where the steps of a process are the same as the prior art, and the only difference is in the recital of the product produced, the process may be properly rejected as anticipated. *In re Sussman*, 141 F.2d 267, 60 USPQ 538, 540-541 (CCPA 1944).

Allowable Subject Matter

6. Claim 10 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

7. **THIS ACTION REMAINS FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group TC 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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